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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/117,071	09/25/1998	ALAN JOHN KINGSMAN	9192.5USWO	3270

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	25

DATE MAILED: 06/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/117,071	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1 ☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3 ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

[illegible] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or [illegible]

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 25.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response filed on 04/09/03 has been acknowledged.

Claims 47-56, 58-61 and 63 are canceled.
Claims 64-74 are newly filed.
Claims 64-74 are pending and are examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim, **must include a complete listing of all claims** in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Claim Rejections - 35 USC § 112

1. Claim 73 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (**new matter**). The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim recites a limitation "at least one primer binding site and at least one integration site". The applicant fails to point out where in the specification there is support for such limitations.

Claim 73 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a producer cell line in vitro by transfecting a set of DNA sequences (pHIT456, PHIT111 and pHT60) wherein the producer cell line produces a

replication defective retroviral particles, does not reasonably provide enablement for a method of making any and all cell type into a producer cells in-vivo such that the producer cells produces a replication defective viral particle that infects target cells in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 12/05/02.

Nature Of Invention:

Invention relates to a method for in-vivo gene delivery.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses making any and all kinds of cells of a subject (in-vivo) a retroviral vector producer cells via introducing three different nucleotides sequences that results in the production of a replication defective retroviral vector, wherein the replication defective retroviral vector produced *in-situ* delivers the heterologous gene to subject's target cells. At best the specification teaches HT1080 producer cells transfected with a set of DNA sequences (pHIT456, PHIT111 and pHT60) that is capable of producing a replication defective retrovirus particle in-vitro (spec page 14-15). The specification as filed fails to disclose that delivery of three sets of nucleotide sequences as claimed into any and all cells of a subject (in-vivo) would transform the target cells into vector producing producer cells, wherein the retroviral particles produced transduce the target cells in-vivo.

State Of Art And Predictability:

The earlier office action provided the evidence that the gene therapy and gene based delivery (in-vivo) is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Therefore they [illegible] create understanding of an underlying mechanism that contribute to a particular disease. Considering the scope of heterologous gene, it is unclear whether the disease would be the result of the loss of

gene product or is the result of altered gene product function. It is even unclear whether the treatment of the disease associated with the heterologous gene would require increase or decrease in the expression of the gene product. Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, in-vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefore would be diluted out before reaching their targets

Response to arguments

The applicant argues that invention as claimed relates to a method of gene delivery and does not purport to achieve medical cure by gene therapy (response, page 5 para.5). The applicant argues that numerous publications and reports of clinical trials have demonstrated successful transfer of genes of interest in human patients (response, page 6). The applicant concluded that office has not provided any reason that similar genes delivered to similar tissues would not be expected to similarly improve patient's clinical parameters (response, page 6).

However, this is not found persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The scope of the claims must bear a reasonable correlation with the scope of enablement (see In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The instant specification fails to disclose a single working example that establishes that delivery of plasmids pHIT456, PHIT111 and pHT60 via

any and all routes of administration (oral, nasal, local or systemic) results in the making of a producer cells in-vivo that produces replication-defective retroviral particles, which infects any and all types of target cells in-vivo to deliver a heterologous gene of interest. Furthermore, the only disclosed utility of the instant invention is gene therapy (spec. page 1; page 5, lines 20-24). The instant specification fails to disclose any other use for the instant invention. Therefore the applicant's assertion that instant claims do not requires any therapeutic effect based upon a gene-based delivery is considered moot. In addition the earlier office action clearly provided the evidence that the gene therapy and gene based delivery are considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. It has been difficult to predict the efficiency and out come of transduced genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors *(supra)*. Even though the applicant argues that state of gene therapy is predictable (in view of an issued patent and other references), the instant specification fails to provide any evidence that upon administration the nucleic acid sequences of constructs pHIT456, PHIT111 and pHT60 ends up in a single cell in vivo that is capable of producing the replication defective viral particles. Each patent application is examined on its own merit and is considered enabled in view of its own disclosure. The issue is not whether the other application support their claims but whether one supports its claims "[i]t is immaterial whether similar claims have been allowed to other" In re Gialito 188USPQ 645,648 (CCPA 1976). The courts have clearly stated that a specification need not to disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required. There is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in*

the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997). In instant case besides calcium phosphate mediated gene transfection into HT1080 cell-line in-vitro the specification fails to provide any evidence that any and all cell types (for example lymphocytes, erythrocytes, osteoblasts etc) in a subject are capable of functioning as producer cells.

Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. The gene based therapies or delivery of heterologous gene of interest using a producer cell in in-vivo are not routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

3. Claim 71 is rejected under 35 U.S.C. 112, second paragraph being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim recites the term "freshly isolated". It is unclear what is fresh in this context. Fresh is relative term and considering the definition provided in the instant specification a cell [illegible] considered fresh in this context.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

S. Kaushal
Patent examiner